Kidney International, Vol. 54, Suppl. 68 (1998), pp. S-60–S-66

Hypertension as cause of end-stage renal disease: Lessons from international registries

FERNANDO VALDERRÁBANO, FRANCISCO GÓMEZ-CAMPDERÁ, and ELIZABETH H.P. JONES

Servicio de Nefrología. Hospital General Universitario "Gregorio Marañón," Madrid, Spain, and ERA-EDTA Registry, London, England, United Kingdom

Hypertension as cause of end-stage renal disease: Lessons from international registries. The incidence of hypertension as cause of ESRD has doubled in the ERA-EDTA Registry in the past two decades, going from 7 to 13%. It is very possible that this is not a real increase in the incidence of hypertension as cause of ESRD, but rather a consequence of greater acceptance of older patients, a phenomenon that has simultaneously occurred. There are geographic differences in the incidence of hypertension as cause of ESRD, from 6% in Japan to 28.5% in the U.S., and 13% in Europe. With the present data, it is impossible to know if these differences are real. The diagnostic criteria used are not uniform and a consensus would be necessary to establish uniform diagnostic criteria for nephrosclerosis or ischemic nephropathy. The percentage of patients starting renal replacement therapy (RRT) with unknown primary renal disease is very different in the U.S. and Europe. This could be a critical factor in explaining these differences. Survival of patients at 5 and 10 years with renal vascular disease did not improve from 1977 to 1989. The same occurs with survival of patients with standard primary renal disease, although this is better than that of patients with renal vascular disease. To interpret this lack of improvement in survival of patients over a decade, we must take into account that at the same time there has been a significant increase in the age of patients starting RRT. Therefore, when the population of patitents of under 55 is analyzed, there is evidence that those starting treatment in the 80's have much better survival than those starting in the 70's. However, survival of patients with renal vascular disease continues to be poorer than that of patients with standard primary renal disease. This lower survival of patients with renal vascular disease seems to be related to higher cardiac mortality, which is in alignment with the diagnosis of hypertension as cause of renal failure.

In the past two decades, there have been significant qualitative changes in the profile of patients starting renal replacement therapy (RRT). The mean age of new patients has increased considerably, such that in different registries in the 90s, a mean and a median age of over 60 can be observed. This change has occurred in parallel to a change in the proportion of the different primary renal diseases causing ESRD. The percentual decrease in some nephropathies, basically glomerulonephritis, is striking, as opposed to the increase in the proportion of patients in whom diabetes and hypertension are the causes of ESRD. It is significant to note that in the USA, 37.4% of new patients are diabetic [1], in Europe this percentage is roughly half [2], whereas Japan [3] comes close to the USA numbers. In the case of hypertension, the situation is similar. From 1977 to 1992 in Europe, the proportion of patients starting dialysis as a consequence of hypertension has tripled over the last years [2].

Key words: hypertension, end-stage renal disease, renal replacement therapy.

RENAL VASCULAR DISEASE AS A CAUSE OF END-STAGE RENAL DISEASE

Data on ESRD consecutive to hypertension are collected in very different ways in the different international registries. The USRDS typifies hypertension and renal artery stenosis as causes of renal failure, but the ERA-EDTA Registry has three codes under which renal failure consecutive to hypertension has been reported over the past years (70, 71, and 72). Code 70 qualifies nonspecific type renal vascular disease, code 71 refers to renal vascular disease due to malignant hypertension, and 72 to renal vascular disease due to hypertension. Other vascular nephropathies and vasculitis appear under different codes.

In the Japanese Registry, the only code included referring to hypertension is nephrosclerosis [3].

INCIDENCE AND PREVALENCE OF RENAL VASCULAR DISEASE IN PATIENTS ON RRT FROM 1976 TO 1995

Table 1 shows the percentage of patients diagnosed with renal vascular disease (codes 70 to 72) in the ERA-EDTA Registry starting RRT in 1977, 1981, 1985, 1989, 1993 and 1995. In 1977 approximately 7% of the patients starting RRT were diagnosed with renal vascular disease, while this percentage has progressively increased in more recent years, reaching nearly 13% in 1995. When the patients are divided according to age groups, in those under 25 the

Table 1. Total number of patients starting renal replacement therapy (T) and patients diagnosed with renal vascular disease (RVD)

	Age				
	0–24	25–44	45–64	>65	Total
1977					
T	1475	4103	5234	1133	11945
RVD	26	232	416	115	789
%	1.76	5.65	7.94	10.1	6.6
1981					
T	1989	5307	8225	2844	18365
RVD	34	287	760	307	1388
%	1.7	5.4	9.24	10.7	7.55
1985					
T	2249	6035	11192	5308	24784
RVD	40	308	1020	734	2102
%	1.77	5.1	9.11	13.82	8.48
1989					
T	2529	7033	13172	8755	31494
RVD	35	361	1267	1362	3025
%	1.38	5.13	9.61	15.5	9.6
1993					
T	1769	5330	10737	10658	28494
RVD	48	280	1083	1963	3374
%	2.71	5.25	10	18.4	11.8
1995					
T	422	1178	2503	2781	6884
RVD	14	66	248	524	870
%	3.31	5.6	9.9	18.8	12.6

Data are from the ERA-EDTA Registry.

Table 2. Total number of male patients starting renal replacement therapy (T) and diagnosed with renal vascular disease (RVD)

	Age				
	0–24	25–44	45–64	>65	Total
1977					
T	852	2570	2992	670	7084
RVD	14	162	301	77	554
%	1.64	6.3	10	11.4	7.8
1981					
T	1169	3262	4748	1638	10817
RVD	21	213	531	198	963
%	1.79	6.52	11.1	12	8.9
1985					
T	1320	3746	6519	2838	14423
RVD	16	212	721	472	1421
%	1.21	5.65	11	16.6	9.85
1989					
T	1442	4393	7922	4836	18593
RVD	21	258	910	888	2077
%	1.45	5.87	11.4	18.3	11.1
1993					
T	1069	3384	6593	6002	17048
RVD	33	184	771	1303	2291
%	3	5.43	11.6	21.7	13.4
1995					
T	260	728	1469	1579	4036
RVD	8	43	175	340	566
%	3	5.9	11.9	21.5	13.9

Data are from the ERA EDTA Registry.

percentages are very low. There is a slight increase in the proportion of patients with renal vascular disease, which does not exceed 3% in 1995. In the 25 to 44 age group there is practically no variation from 1977 to 1995 (ranging between 5 to 6%). The variations are also very slight in the 45 to 64 age group, but the most outstanding finding is in patients over 65, who show a considerable increase, nearly doubled, from 10% in 1977 to 18% in 1995.

When this same data are analyzed according to gender (Tables 2 and 3), the proportion of males starting RRT whose diagnosis of primary renal disease is renal vascular disease is higher than that of females (Fig. 1). In 1995, 14% of the males starting RRT did so as a consequence of renal vascular disease, as compared to 10% of females. These differences are particularly marked in the group of patients over 65. Although females show a considerable increase from 8% in 1977 to over 15% in 1995, the increase in males varies between 12% in 1977 and 22% in 1995.

When the incidence of renal vascular disease in the ERA-EDTA Registry is compared to that of other continental registries, it is significant that the USRDS shows hypertension (including renal artery stenosis) as the cause of ESRD in 28.5% of the patients starting RRT between 1991 and 1995 [1], which is double the figure of 13% observed in the ERA-EDTA Registry in 1995. In Spain, renal vascular disease appears as cause of renal failure in 15% of the patients starting treatment in 1995. It is interesting to note that the diagnosis of nephrosclerosis appears in the Japanese Registry in only 6.2% of the patients starting RRT in 1993 (Fig. 2) [3].

Table 3. Total number of female patients starting renal replacement therapy (T) and diagnosed with renal vascular disease (RVD)

	Age				
	0–24	25–44	45–64	>65	Total
1977					
T	623	1533	2242	463	4861
RVD	12	70	115	38	235
%	1.92	4.56	5.12	8.2	4.83
1981					
T	820	2045	3477	1206	7548
RVD	13	74	229	109	425
%	1.58	3.61	6.58	9	5.63
1985					
T	929	2289	4673	2470	10361
RVD	24	96	299	262	681
%	2.58	4.19	6.39	10.6	6.57
1989					
T	1087	2640	5250	3919	12896
RVD	14	103	357	474	948
%	1.28	3.9	6.8	12	7.35
1993					
T	700	1946	4144	4656	11446
RVD	15	96	312	660	1083
%	2.14	4.93	7.52	14.1	9.46
1995					
T	162	450	1034	1202	2848
RVD	6	23	73	184	286
%	3.7	5.1	7	15.3	10

Data are from the ERA EDTA Registry.

With the progressive increase in age of new patients starting RRT that was 38% of the new patients in the ERA-EDTA Registry being over 65 in 1992 [2] in mind, we have analyzed the incidence of renal vascular disease as a cause of ESRD in aged patients in other registries. As

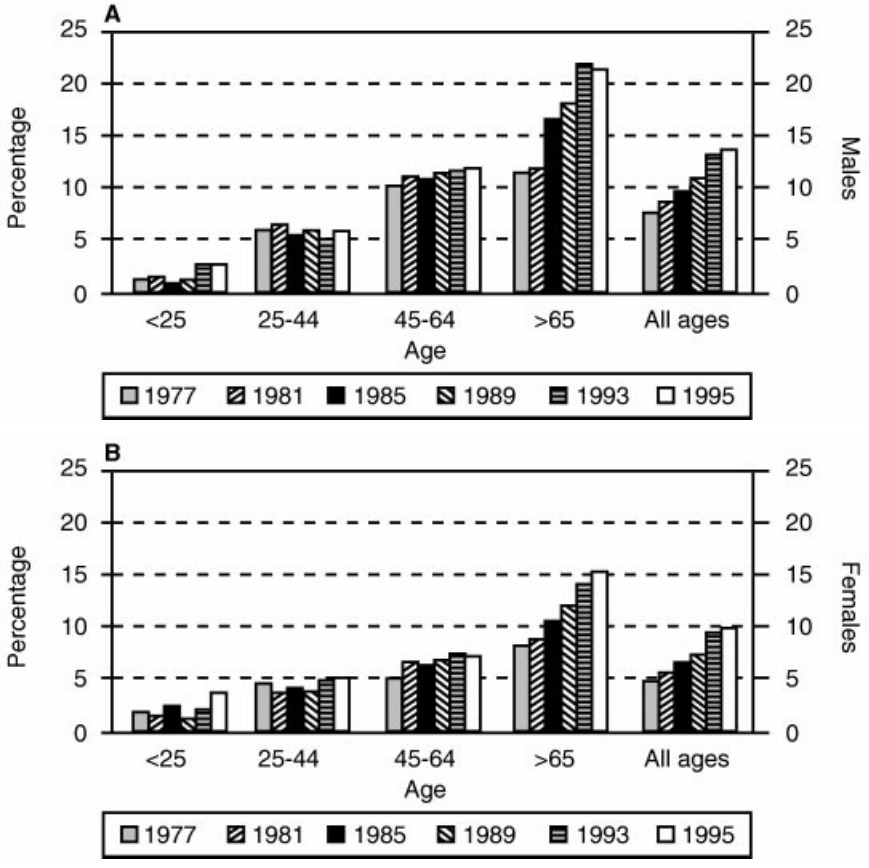

Fig. 1. (*A*) Incidence of renal vascular disease in male patients starting renal replacement therapy from 1976 to 1995 in the ERA-EDTA Registry. (*B*) The same data in female patients. Each block represents the year initiating RRT that is 1977, 1981, 1985, 1989, 1993 and 1995, respectively, left to right.

mentioned earlier, in 1995 in the ERA-EDTA Registry, 22% of males over 65 who started RRT did so as a consequence of renal vascular disease (25% in Spain that same year). However, the USRDS shows that 37.6% of all patients of both sexes over 65 started RRT as a consequence of renal vascular disease [1].

In analyzing the possible reasons for these differences between Europe, the U.S. and Japan, it is crucial to know what criteria were used in making diagnosis of primary renal disease. One important fact is that the percentage of patients starting RRT in whom the diagnosis of primary renal disease is unknown in the USRDS was 4.4% for patients starting between 1991 and 1995 [1], while in the ERA-EDTA Registry the unknown primary renal disease appears as a diagnosis in 17% of the new cases in 1995, a figure that remains quite uniform over the years.

It is evident that if clinical diagnosis is very rigorous, many patients with possible renal vascular disease may appear as having an unknown cause in a registry, while if the clinical diagnosis is less rigorous, the percentage of patients with unknown diagnosis is much lower. Curiously, if the percentage of patients in the USRDS with renal vascular disease (28.5%) is added to those with an unknown diagnosis, a 32.9% figure is obtained, similar to that of the ERA-EDTA Registry when adding the percentage of new patients with renal vascular disease (13%) and unknown diagnosis (17%), that is, 30%. This aspect must be

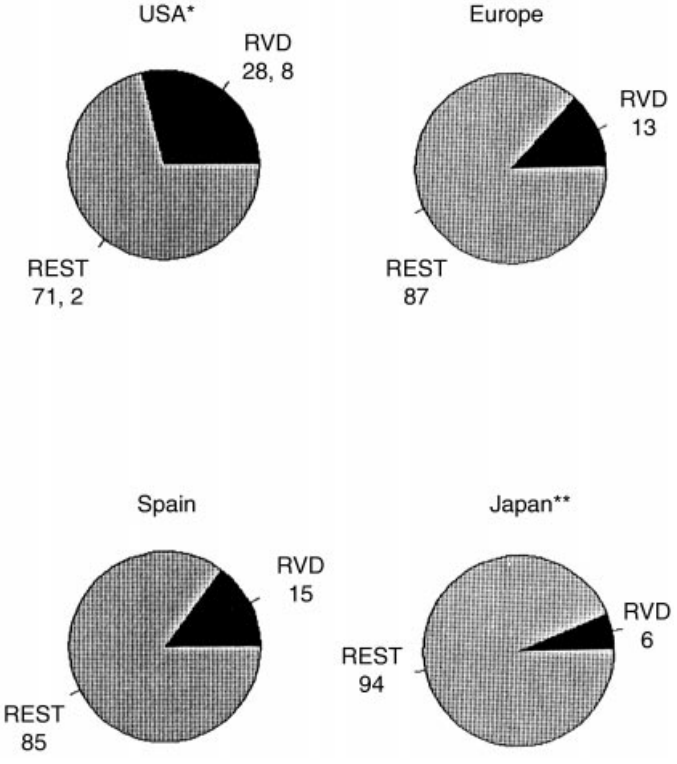

Fig. 2. Incidence of renal vascular disease as cause of ESRD in different national registries. U.S. data are from the USRDS; European and Spanish data from the ERA-EDTA Registry; Japanese data from the Japanese Registry. *1991–1995; **1994.

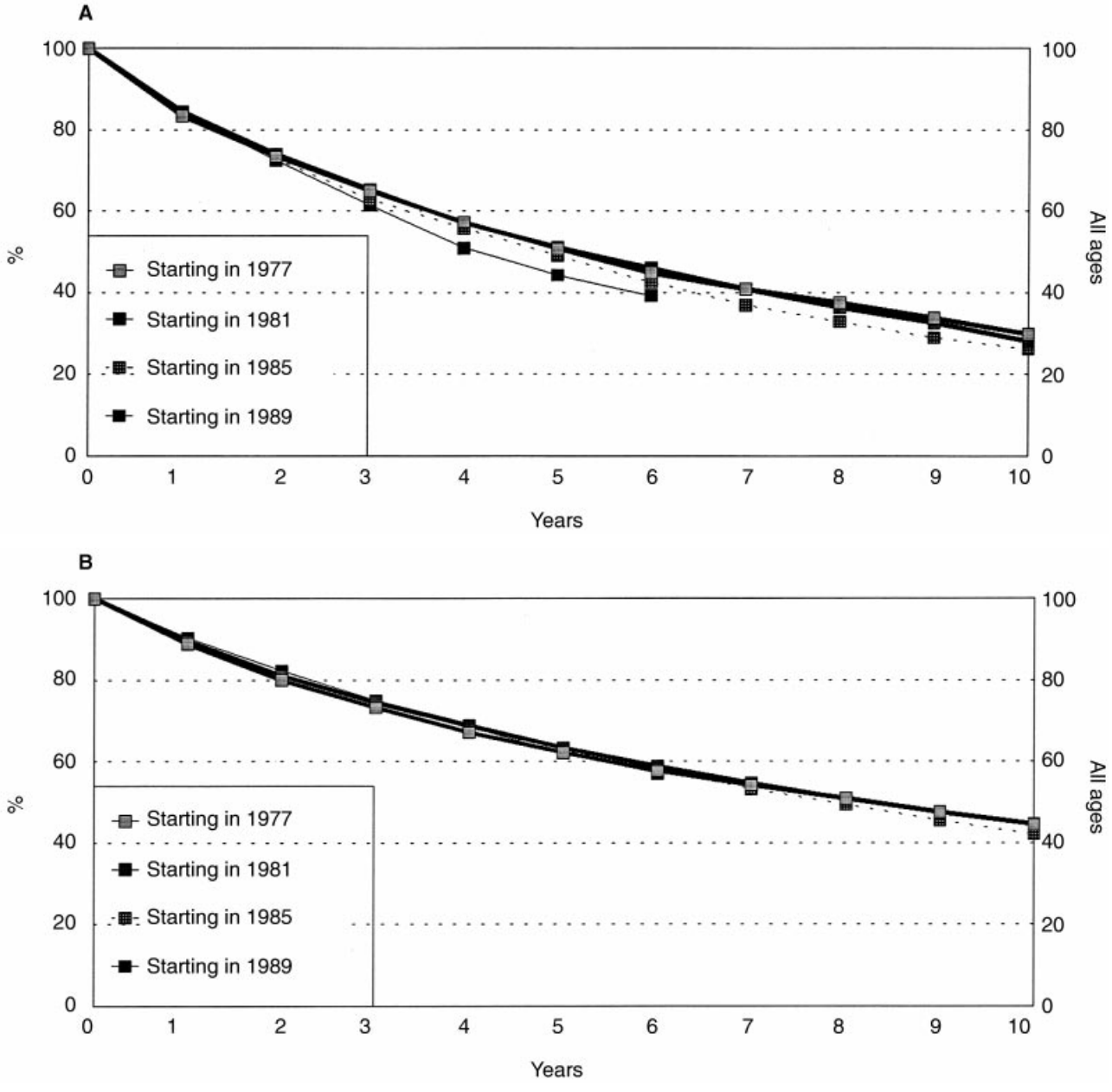

Fig. 3. (*A*) Survival of patients diagnosed with renal vascular disease on renal replacement therapy. All ages of patients of both sexes are included. The survival of four different cohorts of patients is analyzed: patients starting RRT in 1977 ($N = 781$), 1981 ($N = 1352$), 1985 ($N = 2016$) and 1989 ($N = 2849$). Data are from the ERA-EDTA Registry. (*B*) The same data from patients diagnosed with standard renal disease. All ages and patients of both sexes are included. The survival of four different cohorts of patients is analyzed: patients starting RRT in 1977 ($N = 9245$), 1981 ($N = 13193$), 1985 ($N = 16702$) and 1989 ($N = 20012$).

taken into account in future studies analyzing the possible differences in the incidence of renal vascular disease.

In the future, it will be very important to reach an agreement between the different international registries and establish the diagnostic criteria for the different primary renal diseases, especially regarding hypertension. Under these circumstances, it will be possible to learn whether these differences really exist.

With regards to the prevalence of renal vascular disease in patients on RRT in the ERA-EDTA Registry, 8% of the stock of patients on RRT in 1995 had renal vascular disease as primary renal disease (9% in Spain). In comparison, in the USRDS, 24% of patients undergoing treatment from 1991 to 1993 were diagnosed with hypertension as cause of ESRD.

SURVIVAL OF PATIENTS WITH RENAL VASCULAR DISEASE ON RRT

Figure 3A shows the survival rates of patients with renal vascular disease as the primary renal disease when starting

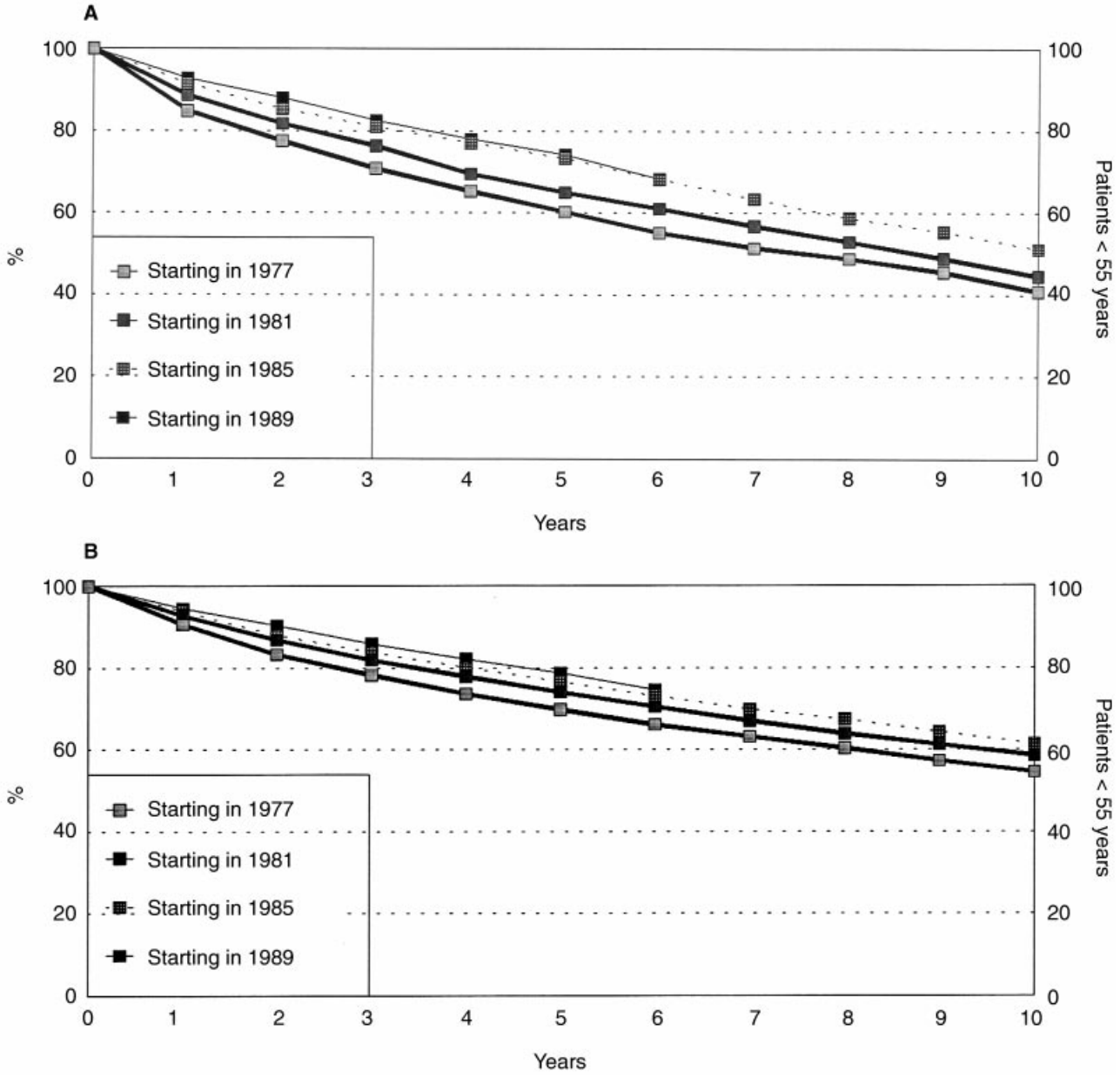

Fig. 4. (*A*) Survival of patients diagnosed with renal vascular disease on renal replacement therapy. Only patients younger than 55 of both sexes are included. The survival of four different cohorts of patients is analyzed: patients starting RRT in 1977 ($N = 482$), 1981 ($N = 670$), 1985 ($N = 702$) and 1989 ($N = 791$). (*B*) Survival of patients diagnosed with standard renal disease on renal replacement therapy. Only patients younger than 55 of both sexes are included. The survival of four different cohorts of patients is analyzed: patients starting RRT in 1977 ($N = 6664$), 1981 ($N = 8420$), 1985 ($N = 9535$) and 1989 ($N = 10456$).

RRT in 1977, 1981, 1985 and 1989. There is no improvement in survival observed during these years, however, there was a slight worsening of survival in the group of patients starting treatment in the most recent year (1989). All patients of all ages and both sexes are included in this analysis.

The ERA-EDTA Registry has frequently used the concept of standard primary renal disease as a comparative model in multiple analyses. Included in the definition of standard primary renal disease are all patients with primitive non-secondary nephropathies. Therefore, this concept groups all types of glomerulonephritis, pyelonephritis and interstitial nephritis, toxic and drug induced nephropathies and cystic diseases.

Figure 3B shows the survival of patients diagnosed with standard primary renal disease of both sexes and all ages who started RRT during the same years (1977, 1981, 1985 and 1989). Actuarial survival observed did not improve in

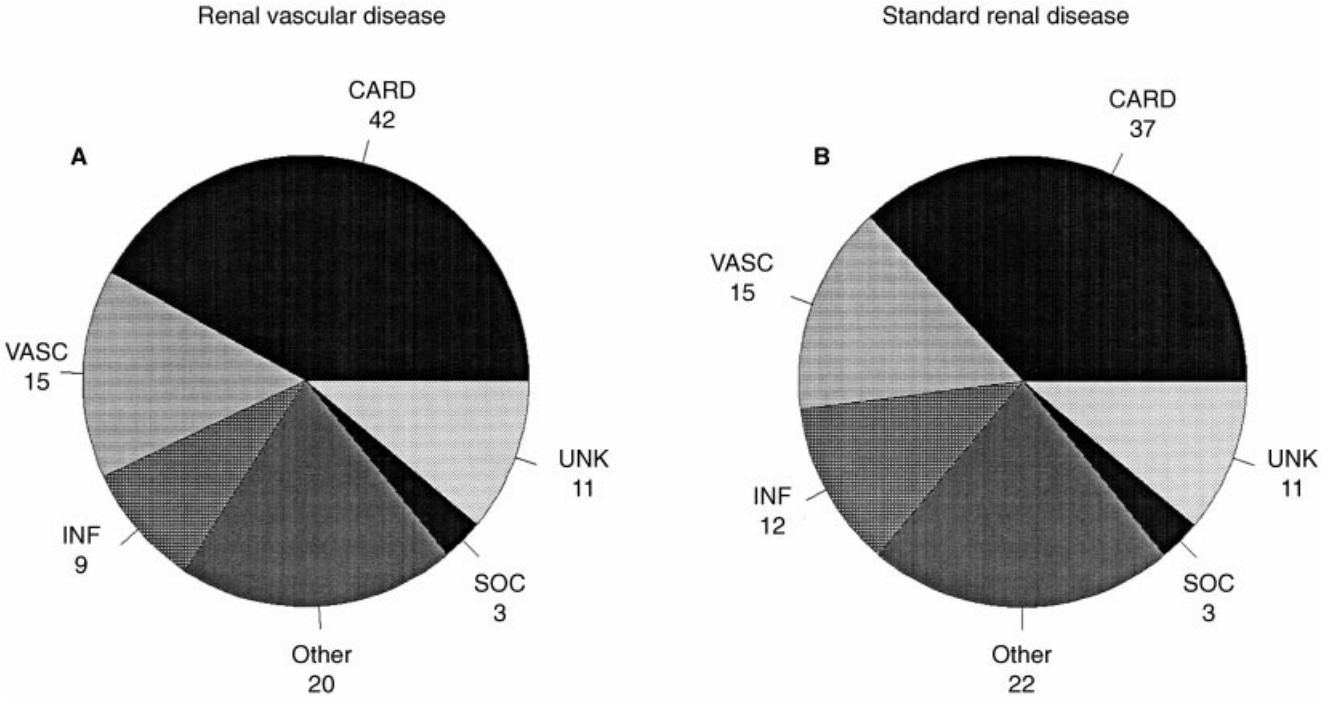

Fig. 5. Percentage of different causes of death in renal replacement therapy patients diagnosed with renal vascular disease and with standard renal disease. Data are the patients reported dead in 1993 to the ERA EDTA Registry. Abbreviations are: CARD, cardiac; VASC, vascular; INF, infections; UNK, unknown; SOC, social (suicide and discontinuation of treatment). Those with renal vascular disease numbered 1959, and those with standard renal disease numbered 8890.

the years analyzed, and remained stable, but is nearly 20% lower at 5 and 10 years in patients with renal vascular disease compared to patients with standard renal disease.

This could give the impression that the results of RRT have not improved over the past decades, but we must take into account that, simultaneously in the years studied, there has been a significant increase in the age of new patients. In effect, in 1977 only 9.5% of all patients starting RRT were over 65. In 1987, 25% were over 65 and in 1992, 38% were over this age [2]. Therefore, when we evaluate survival results, we must take into account that the populations analyzed have varied fundamentally in age and, in effect, when we study a more uniform population, that of patients under 55 starting RRT in 1977, 1981, 1985 and 1989, we can see an improvement both in patients with renal vascular disease (Fig. 4A) and in patients with standard renal disease (Fig. 4B). In each patient population analyzed at the four year difference in time in which they started RRT, actuarial survival is comparatively better than that of the preceding years. In the group of patients under 55 we again observe that survival is worse for patients with renal vascular disease. When we compare survival at 5 and 10 years of the patients starting treatment in 1985 of all ages or under 55, we see better survival rates at 5 and 10 years in those under 55 with standard primary renal disease. This is lower for the same group in cases of renal vascular disease.

CAUSES OF DEATH IN PATIENTS ON RRT

We selected a uniform population, that of patients reported dead to the ERA-EDTA Registry in 1993. In that year, a total of 8,890 patients with a diagnosis of standard primary renal disease and 1,959 patients with renal vascular disease died. When we analyze the percentages of the different causes of death in these cases (Fig. 5), it is most interesting to note that cardiac causes were responsible for death in 42% of the patients with renal vascular disease as compared to 37% of the patients with standard primary renal disease. There is no difference in the other causes of death, with the exception of infections, which show a slightly lower percentage in patients diagnosed with renal vascular disease than in those diagnosed with standard primary renal disease.

This finding is in alignment with the existence of lesser survival in patients with renal vascular disease. The probability of the existence of cardiopathies in these patients is higher and has more repercussions than in patients with standard primary disease.

CONCLUSIONS

In Europe, the incidence of hypertension as a cause of ESRD has doubled (7% to 13%) in the last two decades, in

parallel to the increase in age of new patients. Geographical differences do exist, ranging from an incidence of 6% in Japan to 28.5% in the U.S., however, the diagnosis criteria are not uniform. Concensus among different national registries of renal patients is necessary to standardize clear diagnosis parameters of nephrosclerosis and ischemic nephropathy before national registry data can be validly compared.

Five and ten year survival rates of patients with renal vascular disease is worse than that of patients with standard renal disease. Neither of these survival rates has improved in the last decade. However, survival of patients under 55 has improved in those starting RRT in the 80s, compared to that of patients starting RRT in the 70s. Nevertheless, survival of patients under 55 with renal vascular disease remains worse than that of patients with standard renal disease. The worse survival of patients with renal vascular disease could be related to a higher cardiac mortality in this group of patients.

Reprint requests to Fernando Valderrábano, M.D., Servicio de Nefrología, Hospital General Universitario "Gregorio Marañón," Dr. Esquerdo 46, 28007 Madrid, Spain.
E-mail: valde@bitmailer.net

REFERENCES

1. Excerpts from the USRDS 1997 Annual Data Report. *Am J Kidney Dis* 30(Suppl 1):S40–S53, 1997
2. Valderrábano F, Jones EHP, Mallick NP: Report on management of renal failure in Europe, XXIV, 1993. *Nephrol Dial Transplant* 10(Suppl 5):1–25, 1995
3. Shinzato T, Nakai S, Akiba T, Yamazaki C, Sasaki R, Kitaoka T, Kubo K, Shinoda T, Kurokawa K, Marumo F, Sato T, Maeda K: Current status of renal replacement therapy in Japan: Results of the annual survey of the Japanese Society for Dialysis Therapy. *Nephrol Dial Transplant* 11:2143–2150, 1996